293. *The Crystal Structure of* (−)-*Aspidospermine* N(b)-*Methiodide.*

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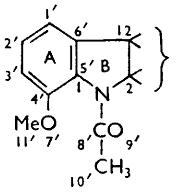
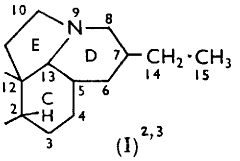
A three-dimensional *X*-ray crystal structure analysis of the *N*(*b*)-methiodide of the alkaloid aspidospermine shows the molecular structure to have been correctly ascertained by chemical methods apart from the location of one ethyl group.

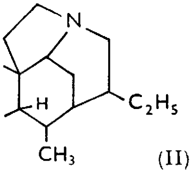
The alkaloid aspidospermine obtained from the bark of *Aspidosperma quebracho-blanco* Schlect. was first examined chemically by Ewins [1] in 1914, but serious attempts to elucidate its molecular structure did not begin until about 1947 when it was taken up independently by Openshaw and Smith [2] in Britain and by Witkop and his co-workers [3] in the United States. Conroy and his co-workers [4] have also made contributions.

It was clear by the early part of 1958 that, although much was known concerning the molecular structure, its unequivocal assignment by purely chemical methods would be difficult. When *X*-ray analysis was first contemplated the four currently acceptable structures were (I—IV). Towards the completion of the *X*-ray structure analysis, Conroy and his co-workers,[5] unaware of our work, withdrew their two structures (III) and (IV) which alone contain *N*-methyl groups.

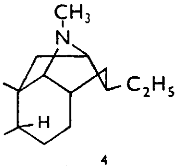




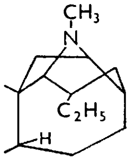
(I)[2,3]



(II)[3]



(III)[4]



(IV)[4]

A preliminary *X*-ray crystallographic examination of deacetylaspidospermine *N*(*a*)-methobromide (quaternized at $N_{(1)}$) showed the bromide ions to be unfavourably sited in the unit cell for phase assignment. Fearing this might also be the case with other halide derivatives involving the quaternized *N*(*a*) atom, Dr. G. F. Smith, Manchester University, kindly prepared and submitted a suitable crystalline specimen of the *N*(*b*)-methiodide (quaternized at $N_{(9)}$) on which crystal structure analysis was carried out. The corresponding methobromide, which would have been more satisfactory for *X*-ray analysis, defied attempts at crystallization.

The colourless crystals of molecular formula, $C_{23}H_{33}N_2O_2I$ (M, 496), m. p. 267° (decomp.), belong to the orthorhombic bipyramidal class, symmetry *mmm*. The acicular crystals crystallized from ethanol have y as the needle axis with {201} and {210} forms developed. The unit-cell parameters are $a = 24{\cdot}3$, $b = 8{\cdot}50$, and $c = 11{\cdot}1$ Å, the volume of the unit cell being 2293 Å^3. The crystal density evaluated by flotation in carbon tetrachloride–dioxan was 1·456 g. ml.$^{-1}$. For $Z = 4$ molecules in the unit cell, the calculated density, D_c, is 1·438 g. ml.$^{-1}$, whence $F(000)$ the number of electrons per unit cell is 1026. The space group is $P2_12_12_1$ ($D_2{}^4$, No. 19). Cu-$K\alpha$ radiation was used throughout for which

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[1] Ewins, *J.*, 1914, **105**, 2738.
[2] Openshaw and Smith, 13th Internat. Congress, I.U.P.A.C., 1953, Abs., p. 223.
[3] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1954, **76**, 5603.
[4] Conroy, Brook, Rout, and Silverman, *J. Amer. Chem. Soc.*, 1957, **79**, 1763.
[5] Conroy, Brook, Rout, and Silverman, *J. Amer. Chem. Soc.*, 1958, **80**, 5178.

the linear absorption coefficient μ is calculated as 123·4 cm.$^{-1}$. The crystals used were all less than 0·1 mm. in their maximum dimension and no absorption corrections were made.

The x,y co-ordinates of the iodide ions were unambiguously established from the z-axis Patterson projection. The Fourier projection derived from this was unintelligible apart, of course, from the confirmed positions of the iodide ions. The resolution, as might be expected, was too poor for any allocation of atomic positions to be possible. The x-axis Patterson and Fourier projections were similar, merely allowing the y,z co-ordinates of the iodide ions to be established.

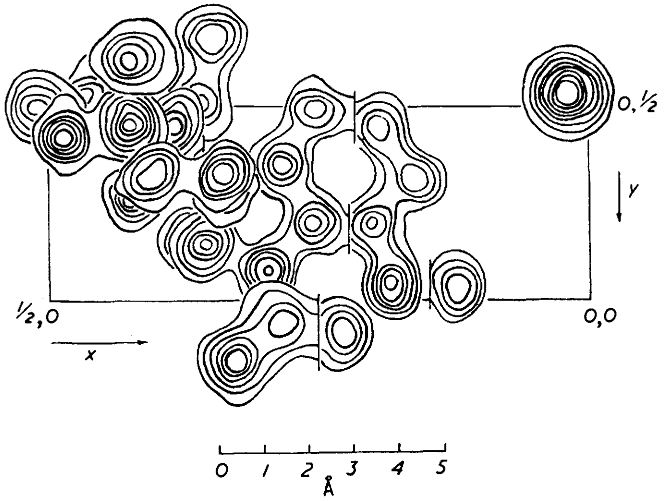

FIG. 1. *Composite electron-density map viewed along the z-axis.*

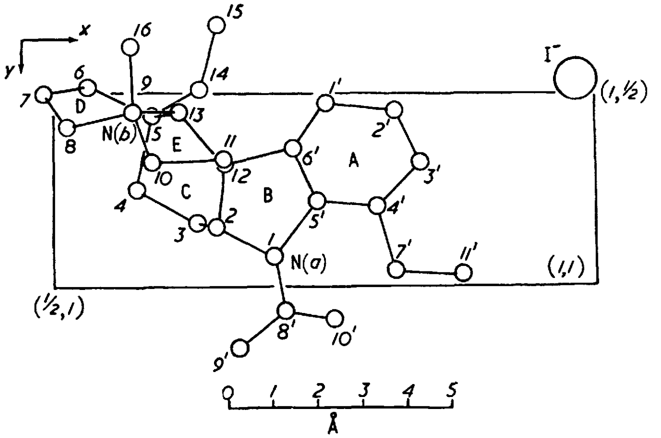

FIG. 2. *Atomic positions corresponding to Fig.* 1.

Data for a three-dimensional analysis were collected by equi-inclination Weissenberg photographs and, in order to keep the measurements and computational effort to a minimum, no reflexions were estimated for which sin θ >0·77. Of these 1095 reflexions the intensities of 958 were observed. The Wilson method [6] was used for evaluation of approximate absolute scale and temperature factors. The average temperature factor found was $B = 3{\cdot}0$ Å^2.

There is no centre of symmetry in the space group $P2_12_12_1$; asymmetric molecules of one hand cannot in any case crystallize in centrosymmetric space groups. With the origin

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[6] Wilson, *Nature*, 1942, **150**, 152.

given in the *International Tables*,[7] the co-ordinates of one iodide ion are 0·982, 0·473, 0·046. Phases calculated on the basis of the iodide ions only were assigned to the structure factors and a three-dimensional electron-density plot evaluated on a Deuce computer at intervals of 1/80 along x and 1/20 along y and z.

The peaks on the electron-density plot could be divided into three categories: (i) those of magnitude $>1{\cdot}8$ e.Å^{-3} which appeared to correspond to rationally bonded atoms (23 in number), (ii) those of magnitude $<1{\cdot}8$ e.Å^{-3} for which a rational bonding scheme could be devised (3 in number), and (iii) those of magnitude $<1{\cdot}8$ e.Å^{-3} for which no rational assignment of chemical bonds could be devised (5 in number). The peaks of category (i) established without doubt the structure of the main bulk of the molecule and appeared to support formula (I). If the molecular formula of the methiodide is correct, 27 carbon, nitrogen, and oxygen peaks are expected and the four which did not appear in category (i) were $C_{(6')}$, $C_{(4)}$, $C_{(15)}$ [which appeared in category (ii)] and one of either $C_{(10')}$ or $O_{(9')}$. Structure factors and phases were re-computed by including, in addition to iodide ions, the 23 peaks of category (i). The indole nitrogen atom $N_{(1)}$ and methoxy-oxygen atom $O_{(7')}$ were given their due weight but all other atoms were taken equivalent to carbon. The residual fell from 0·35 (iodide ions only) to 0·25.

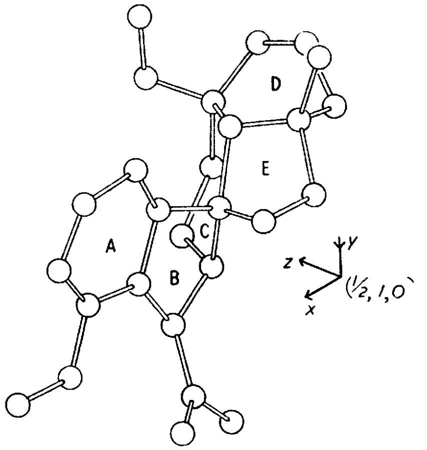

FIG. 3. *Scale drawing of molecule with atomic positions as found.*

The new electron-density map based on these new phases revealed 21 of the 23 included atoms with enhanced electron density, but two had weakened, $C_{(14)}$ and $C_{(11')}$. The latter, however, was replaced by a new peak, evidently the correct methoxy-carbon atom. Both $C_{(6')}$ and $C_{(4)}$, omitted from the phase calculation, showed up clearly. In addition so did either $C_{(10')}$ or $O_{(9')}$, but less sharply. New phases and structure factors were calculated by using what were now assumed to be the 27 atoms of the molecular structure and a new electron-density plot computed. The residual fell from 0·25 to 0·24.

At this stage the interpretation of the electron-density map became difficult. The first disturbing feature was the weakening of $C_{(14)}$ and virtual disappearance of $C_{(15)}$ and their close proximity to a neighbouring molecule (although small shifts in position during refinement might overcome this). It was difficult to believe that the peak for $C_{(14)}$ was spurious since it had appeared on the first electron-density map without being included in the calculation of phases, and, moreover, its position was just that supported by chemical evidence. Against this was the argument that if this peak were genuinely that for $C_{(14)}$ this assignment would leave a large unfilled hole in the crystal structure in the neighbourhood of $C_{(5)}$. However, in this hole there were two electron-density peaks of low magnitude

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[7] "International Tables for X-ray Crystallography," Kynoch Press, Birmingham, 1952, Vol. I, p. 105.

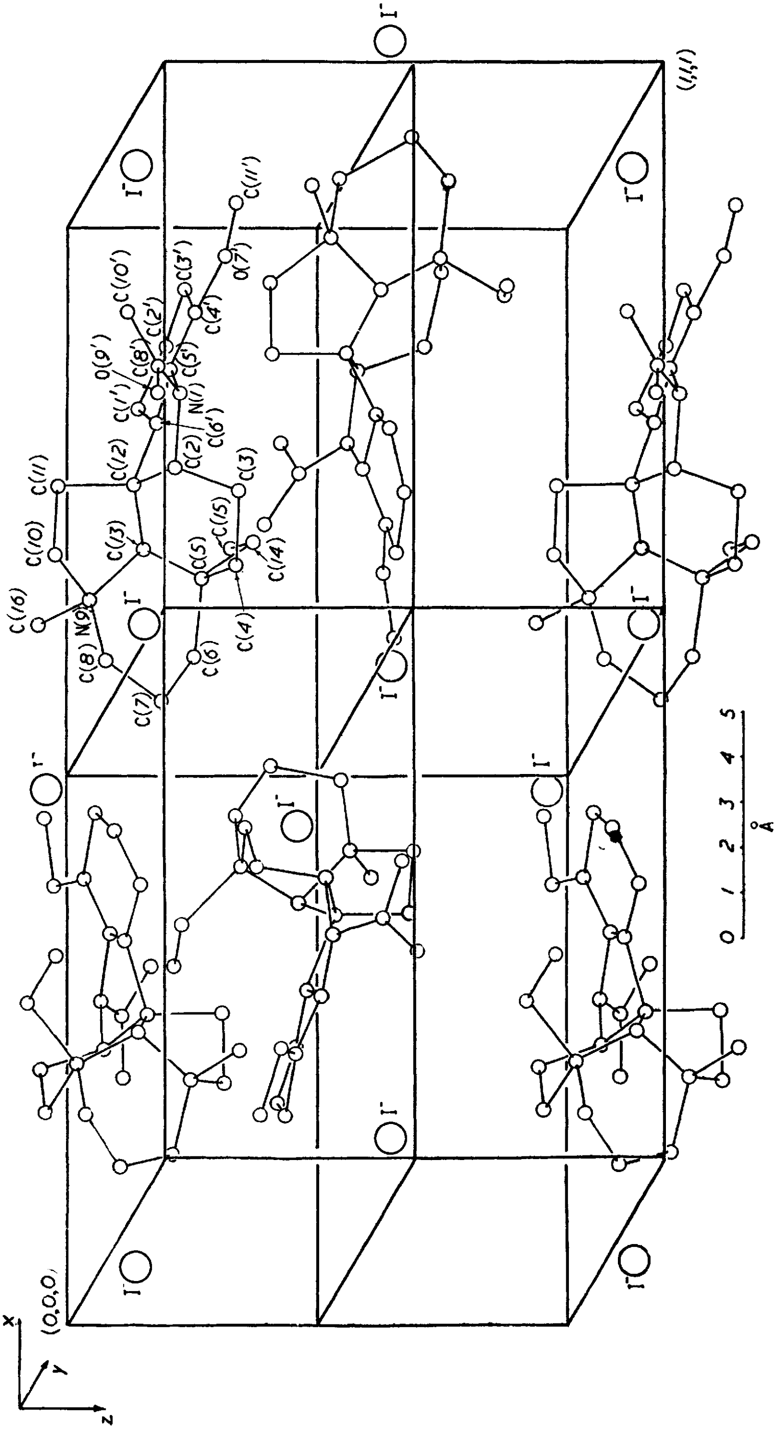

FIG. 4. *General view of crystal structure.*

and it was at one stage thought that these might be due to two of the three carbon and oxygen atoms of occluded ethanol. Its presence would not significantly alter the chemical analysis if present in 1 : 1 molar ratio. However, a careful comparison of the unit cell with that of a crystal specimen crystallized from dimethylformamide revealed no differences in parameters and no change in *X*-ray intensities. Moreover, the infrared spectra of the two specimens were identical in the range 3—15 μ.

It was decided to test whether the two peaks in the $C_{(5)}$ region could be genuine by including them with the 27 other atoms in a new set of structure factor calculations. It was found that the residual *improved*, dropping from 0·24 to 0·23.

The final confirmation that the originally assigned $C_{(14)}$ and $C_{(15)}$ peaks were erroneous was given by the marked improvement in residual when these were removed from the structure-factor calculations, leaving, of course, the new carbon atoms in the $C_{(5)}$ region. The residual fell from 0·23 to 0·209 and the electron density map was gratifyingly free from false peaks. The conclusion was therefore inescapable that the ethyl group is not attached to $C_{(7)}$ as shown in formula (I), but is in fact attached to $C_{(5)}$.

Discussion.—A composite electron-density section map is shown in Fig. 1. This was computed by using phases calculated from the atomic co-ordinates given in the Table and allows an unambiguous assignment of atoms to be made as shown in Fig. 2. This view of the molecule makes it difficult to appreciate its conformation, which is shown from a different angle in Fig. 3. [For conventional chemical formulation see formula (II) of the following paper.[8]]

Fractional atomic co-ordinates of molecule shown in Figs. 1 *and* 2.

	x	*y*	*z*		*x*	*y*	*z*		*x*	*y*	*z*
I^-	0·982	$0{\cdot}47_3$	0·046	C(10)	0·596	$0{\cdot}68_0$	$\overline{0{\cdot}154}$	C(3′)	0·841	$0{\cdot}68_5$	0·100
N(1)	0·706	$0{\cdot}92_5$	0·045	C(11)	0·659	$0{\cdot}67_5$	$\overline{0{\cdot}150}$	C(4′)	0·800	$0{\cdot}80_0$	0·100
C(2)	0·650	$0{\cdot}85_0$	0·053	C(12)	0·659	$0{\cdot}68_7$	0·000	C(5′)	0·748	$0{\cdot}79_5$	0·051
C(3)	0·633	$0{\cdot}83_5$	0·182	C(13)	0·621	$0{\cdot}55_0$	0·044	C(6′)	0·720	$0{\cdot}65_1$	0·050
C(4)	0·579	$0{\cdot}73_5$	0·195	C(14)	0·638	$0{\cdot}49_0$	0·274	O(7′)	0·818	$0{\cdot}96_5$	0·128
C(5)	0·594	$0{\cdot}56_0$	0·165	C(15)	0·654	$0{\cdot}33_0$	0·253	C(8′)	0·715	$1{\cdot}05_8$	$\overline{0{\cdot}025}$
C(6)	0·535	$0{\cdot}48_0$	0·160	C(16)	0·576	$0{\cdot}38_3$	$\overline{0{\cdot}133}$	O(9′)	0·672	$1{\cdot}15_5$	$\overline{0{\cdot}043}$
C(7)	0·493	$0{\cdot}50_0$	0·093	C(1′)	0·755	$0{\cdot}52_0$	0·040	C(10′)	0·768	$1{\cdot}08_0$	$\overline{0{\cdot}088}$
C(8)	0·516	$0{\cdot}58_5$	$\overline{0{\cdot}035}$	C(2′)	0·806	$0{\cdot}56_0$	0·088	C(11′)	0·879	$0{\cdot}97_0$	0·150
N(9)	0·578	$0{\cdot}54_5$	$\overline{0{\cdot}060}$								

The analysis is of too low an accuracy for a detailed discussion of the stereochemistry to be possible. One can note the chair conformation of ring C and the boat conformation of ring D (ring D is also thought to have the chair conformation in the free base; see following paper [8]). As to rings A and B, if one takes atoms $C_{(5')}$ and $O_{(6')}$ and the midpoint of $C_{(2')}$–$C_{(3)}$ as adequately defining the plane of the benzene ring, then $C_{(12)}$ lies 0·16 Å out of this plane in one direction and $N_{(1)}$ lies 0·16 Å out of it in the other, with $C_{(2)}$ intermediate in position. This rather surprising result must be regarded with caution, especially as the close proximity of an iodide ion to the benzene ring will make the positional errors in the benzene peaks exceptionally high. One would have expected, nevertheless, that the bonds attached to the benzene ring would have been more nearly coplanar with it.

The $N_{(1)}$-acetyl group is coplanar with the nitrogen atom and noticeably bent out of the indole mean plane by the pyramidal requirements of the nitrogen atom.

The packing of the molecules is shown in general view in Fig. 4. The alkaloid ions can be considered to form thick layers and the iodide ions to form layers between them. The ends of the bulky organic cations obtrude into the spaces between the iodide ions.

There are no unusually short intermolecular distances save perhaps that of 3·2 Å between one terminal atom of the acetyl group and the *N*-methyl atom, $C_{(16)}$, of an adjacent molecule. On these grounds we have taken this acetyl atom in the Table to be the oxygen

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[8] Smith and Wróbel, following paper.

atom rather than the more bulky methyl group. Its peak density is also higher (see Fig. 1). Again inaccuracies in the analysis could make this the wrong assignment.

The computations were carried out on the Deuce computer at the English Electric Company, Stafford. It is a pleasure to acknowledge the help given by Mr. M. R. Wetherfield and the generosity of the English Electric Company in providing facilities. The work, which was carried out in fulfilment of the M.Sc. (Manchester) degree, was made possible by financial help to J. F. D. M. from the Distillers Company Limited and the Harrison Memorial Fund. Manchester University also gave generous help with expenses incurred. Finally our thanks are offered to Dr. G. F. Smith for suggesting the problem to us and for preparing crystal specimens to our requirements.

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